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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/674,087	09/29/2003	Jianzhu Chen	0492611-0507 (MIT 10396)	2178

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EXAMINER	
ASHEN, JON BENJAMIN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 10/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/674,087	CHEN ET AL.	
	Examiner	Art Unit	
	Jon B. Ashen	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *01 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,23-90,98 and 99* is/are pending in the application.

4a) Of the above claim(s) *1-20,23-37,43-48 and 50-80* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-42,49,81-90,98 and 99* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/04; 09/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group IV, claims 38-49, 63-71, 81-90 and 96-97, "cationic and modified cationic polymers" and "siRNAs" in the reply filed on 08/01/05 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Status of the Application

2. Claims 1-20, 23-90, 98 and 99 are pending in this application. Claims 1-20, 23-37, 43-48 and 50-80 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 21-22 and 91-97 were cancelled by Applicant in the communication filed 08/01/05. Claims 38-42, 49, 81-90, 98 and 99 are currently under examination.

Information Disclosure Statement

3. Reference EP 1144623 on the information disclosure statement filed 09/12/2005 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of this

patent as listed, that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered.

Additionally, the following references on the IDS filed 09/12/05 are duplicates of references submitted on the IDS filed 12/28/2004: Bitko et al. 2001, Gautam et al. 2000 and Gitlin et al. 2002. They have been considered on the IDS filed 12/28/05 and are lined thru on the IDS of 09/12/05 to avoid the appearance of duplicate references on the face of any patent that may issue from this application.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 38-42 and 49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 38-42 and 49 depend from withdrawn claim 23 which itself, depends from withdrawn claim 1.

6. Claims 38-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 38 is drawn to a method of inhibiting a target transcript in a mammalian subject comprising administering a composition to the respiratory system of a subject by introducing the composition into the vascular system

of the subject. However, the skilled artisan cannot determine the metes and bounds of what is being claimed with this terminology, without assumption, because it is not clear how introducing the composition into the vascular system of the subject is administering a composition to the respiratory system of a subject.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 38-42, 49, 81-90, 98 and 99 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 38, 40-42 and 81-83 are drawn to a method of inhibiting a target transcript in a mammal comprising administering a composition comprising an RNAi inducing entity targeted to a target transcript and a delivery agent that is a cationic or modified cationic polymer. Claims 39, 49, 84-90, 98 and 99 are drawn to a method of treating or preventing a disease in any subject wherein the disease or condition is associated with overexpression or inappropriate expression of any transcript or excessive functional activity of any polypeptide encoded by the transcript, comprising

administering to or delivering to a subject at risk of or suffering from a disease or condition (as above), a composition comprising an RNAi inducing entity targeted to a target transcript and a delivery agent that is a cationic or modified cationic polymer. Further limitations of dependent claims include wherein administration is by intravenous injection (claims 40, 87), by conventional fluid delivery (claim 41, 88), wherein the RNAi inducing entity comprises an siRNA (claim 42), wherein the solid organ is a lung (claim 39), wherein administration inhibits expression of the target transcript in the lung (claim 82), or at least one tissue or organ other than the lung, in addition to or instead of the lung (claim 83), wherein administration is by inhalation or intranasally (84), wherein the composition is administered as an aerosol (claim 86), wherein the delivery agent comprises a delivery enhancing moiety to enhance delivery to a cell of interest (claim 89), wherein the delivery enhancing agent comprises an antibody, antibody fragment or ligand (claim 90), wherein the RNAi inducing entity comprises a modified nucleotide (claims 98 and 99).

All of the instant claims read broadly on *in vivo* methods of preventing or treating any disease or condition associated with overexpression or inappropriate expression of any transcript or excessive functional activity of any polypeptide comprising administering to or delivering to any subject at risk of or suffering from a disease or condition (as above), a composition comprising any RNAi inducing entity targeted to any target transcript and a delivery agent that is a cationic or modified cationic polymer. Claims 89 and 90 reads broadly on the instant methods wherein the delivery agent comprises a “delivery enhancing moiety,” which can be any antibody, antibody fragment

or ligand that enhances delivery to a "cell of interest", which can be any cell. However, the specification as filed does not provide an adequate written description of the RNAi inducing entity that is required to practice the instantly claimed methods, that will function, *in vivo*, to reduce the expression of any target transcript in any organism, including mammals, or that will prevent or treat any disease or condition that is associated with overexpression or inappropriate expression of any transcript or excessive functional activity of any polypeptide with overexpression, commensurate with the breath of what is now claimed,

The specification as filed provides no limiting definition of what is encompassed by "an RNAi inducing entity" wherein it discloses that an RNAi inducing entity encompasses RNA molecules whose presence in the cell results in RNAi and leads to reduced expression of a target transcript, which specifically includes siRNA, shRNA and RNAi-inducing vectors (pg. 12). The specification as filed provides only general guidance in regards to what is encompassed a target transcript that is associated with overexpression or inappropriate expression thereby resulting in a disease or condition (which can be any disease or condition) (pg. 8-9). The specification discloses that the instantly claimed methods are generally directed to inhibiting the expression of any target transcript *in vivo*, in any subject, using siRNA to mediate RNAi to provide a treatment. The specification discloses that, "As used herein, treating includes reversing, alleviating, inhibiting the progress of, preventing, or reducing the likelihood of disease disorder or condition to which such term applies, or one or more symptoms or manifestations of such disease, disorder or condition" (pg. 15). The specification

discloses limited examples of methods of inhibiting the expression of a target transcript *in vivo*, in a mouse, using siRNA targeted to influenza virus NP and PA mRNAs that are complexed with the cationic polymer, polyethyleneimine (PEI) and injected into the retro-orbital vein of mice (pg. 74).

Therefore, in disclosing only broad and general guidance in regards to what is encompassed by "an RNAi inducing entity" and "a target transcript" and only limited examples of an *in vivo* method of inhibiting gene expression of viral mRNAs in a mouse, the specification does not provide a correlation between the structure of the claimed RNAi inducing entity (that can be any RNA molecule whose presence in the cell results in RNAi and leads to reduced expression of a target transcript wherein the target transcript is any target transcript) and the function as claimed, that will, upon administration with a delivery agent (that is a cationic polymer or modified cationic polymer, that is PEI, inhibit or prevent the expression of any target transcript, *in vivo*, in any organism (including mammals). Neither does the specification as filed provide a correlation between the structure of the claimed delivery enhancing moiety and the function of being any moiety that will enhance delivery to any cell of interest wherein the delivery enhancing agent can be any antibody, any antibody fragment or any ligand, commensurate with the breadth of what is claimed. Additionally, the specification as filed does not disclose any distinguishing identifying characteristics of an RNAi inducing entity, a target transcript or a delivery enhancing agent that is an antibody, antibody fragment or ligand that would indicate that applicant was in possession of these broadly claimed genera, commensurate with what is now claimed, that will function in the

instantly claimed methods of inhibiting the expression of any target transcript *in vivo* in any organism or in a method of treatment (including prevention) in any organism, *in vivo*.

The specification does not provide the specific guidance that would be required to reasonably lead one of skill in the art to the instant invention or that would allow the skilled artisan to recognize that Applicant was in possession of the instant invention, commensurate with the breadth of what is now claimed: that will function to inhibit the expression of any target transcript *in vivo* in any organism or to provide a treatment (including to prevent) in any organism, *in vivo*, of any disease or condition associated with over or inappropriate expression of a target transcript or inappropriate or excessive expression or activity of a polypeptide encoded by the transcript.

The state of the art cannot provide the required specific guidance, as evidenced by Elbashir et al. 2001 (Reference 2, Form PTO 1449, filed 4/21/05 in this application) who provide a only a general outline for the construction of interfering RNAs (siRNAs) and point out that target recognition for interfering RNAs is highly sequence specific and that the nucleotide sequence at the target site and/or the accessibility of the target RNA structure may be responsible for variations in efficiency observed in their experiments with siRNA (pg. 6885, col. 2).

MPEP § 2163[R-2] I. states:

> To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., > Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003);< Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116.

> The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., Vas-Cath, Inc., 935 F.2d at 1563-64, 19 USPQ2d at 1117.
>
> Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").
>
> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. > Enzo Biochem, 323 F.3d at 964, 63 USPQ2d at 1613.<

In the instant case, Applicant has not provided adequate written description of their invention because the specification does not convey, with reasonable clarity to those of skill in the art, as of the filing date sought, that applicant was in possession of the invention now claimed. Applicant has not shown how the invention was "ready for patenting" such as by the disclosure of the structure of "an RNAi inducing entity" that inhibited the transcription of any "target transcript" wherein it is administered with any "delivery enhancing moiety" to any "cell of interest" that would function commensurate with the breadth of what is now claimed (that shows that the claimed invention was complete), or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the broad genus of methods as claimed. What, in particular, is the structure of an RNAi inducing entity that would target any target transcript, that is administered with any delivery enhancing moiety that enhances

delivery to any cell of interest that would be required to practice the method of the instant invention in its full breadth, that will function to inhibit the expression of any target transcript *in vivo* in any organism or to provide a treatment (including to prevent) in any organism, *in vivo*, of any disease or condition associated with over or inappropriate expression of a target transcript or inappropriate or excessive expression or activity of a polypeptide encoded by the transcript.

9. Claims 38-42, 49, 81-90, 98 and 99 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting, *in vivo*, in a mammal, the influenza virus NP or PA target transcript comprising administering, by intravenous injection to a mouse retro orbital vein, compositions comprising the cationic polymer, PEI, complexed siRNAs of the invention that are NP-1496 and PA2087 siRNAs, does not reasonably provide enablement for the full scope of what is claimed, that encompasses methods of inhibiting any target transcript in any organism and or for any method of treatment as claimed, which, based on the disclosure of the specification as filed (see pg. 15, [0057]), read on methods of preventing in any organism (including mammals and humans), *in vivo*, any disease or condition associated with over or inappropriate expression of a target transcript or inappropriate or excessive expression or activity of a polypeptide encoded by the transcript comprising administering a composition comprising any RNAi inducing agent and any cationic or modified cationic polymer (including wherein the composition comprises any delivery enhancing moiety that enhances delivery to any cell of interest).

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

In the instant case, claims 38-42, 49, 81-90, 98 and 99 are broadly drawn and read on a method of inhibiting a target transcript *in vivo* in any organism, including mammals and on methods of preventing *in vivo*, in any organism including mammals, any disease or condition associated with overexpression or inappropriate expression of any transcript or excessive functional activity of any polypeptide encoded by that transcript using a composition comprising an RNAi inducing entity targeted to a target transcript and a delivery agent that is a cationic or modified cationic polymer. The nature of the invention indicates that the instantly claimed method is a form of nucleic acid therapy, in particular a form of inducing RNA interference, and is subject to the same considerations and limitations as other types of nucleic acid therapeutics (as discussed further below). Moreover, all instant claims drawn to treatment are reasonably interpreted, in light of the specification (treatment is defined by the specification as

including prevention: see pg. 15, [0057]), to read on prevention. Prevent, as defined by Webster's II New Riverside University Dictionary, is defined as, 1. *To keep from happening: Avert.* (pg. 933).

The specification provides no definition of prevention. Applying the dictionary definition to prevent, a reasonable interpretation of the nature of an invention that is a method of preventing a disease or condition as claimed comprising administering a composition comprising any RNAi inducing agent and any cationic or modified cationic polymer (including wherein the composition comprises any delivery enhancing moiety that enhances delivery to any cell of interest) considers that practicing such a method will keep the disease or condition as claimed from happening, now or anytime in the future, including in a subject that is only at risk of the disease or condition as claimed. The specification as filed, however, provides no enabling disclosure which would support claims to a method of prevention.

In regards to the amount of direction provided by Applicant as to how one of skill in the art would practice the full scope of the claimed invention, the specification as filed discloses a method of inhibiting, *in vivo*, in a mammal, the influenza virus NP or PA target transcript comprising administering, by intravenous injection to a mouse, compositions comprising the cationic polymer, PEI, complexed siRNAs of the invention that are NP-1496 and PA2087 siRNAs. Applicant provides no examples of a method of treating or preventing, *in vivo*, in any organism, any disease or condition as claimed using a composition, as claimed. The specification provides only broad and general guidance in regards to what is encompassed by delivery enhancing moieties and cells

of interest and no examples of methods of treating or preventing diseases or conditions as claimed comprising administering the claimed compositions. No enabling disclosure of methods of specific delivery that would allow specific targeting of any target transcript , *in vivo*, in any organism including mammals, comprising administering the composition required by the instant claims, could be found in the specification as filed. Injection of the composition required by the instant claims, into the retro-orbital vein of a mouse, is reasonably interpreted as a systemic administration to the bloodstream and would be reasonably expected to provide non-specific delivery to all tissues and organs that are perfused by the blood; e.g., the highly vascularized lung.

With regard to a method of inhibiting a target transcript, the specification does not provide sufficient guidance for selecting the target transcript, nor does the specification disclose the appropriate route of administration, amount of the RNAi inducing entity and delivery agent that would be required, the identity of the delivery enhancing agent or how one of skill would recognize a "cell of interest" such that a sufficient amount of claimed composition would be taken up (or delivery enhanced), *in vivo*, by particular cells of interest, tissues or organs and effectively inhibit any target transcript. With regard to a method of treatment or prevention, the specification does not provide guidance as to which target transcripts can be targeted by the instantly claimed methods, wherein the target transcript can be any target transcript in any organism, that would provide a treatment or that would prevent, *in vivo*, any disease or condition as claimed. The specification does not provide representative working examples (beyond those shown in mouse) of target transcripts, within the scope of the method of the

invention as claimed, that are any target transcripts in any organisms that are associated with any disease or condition as above, the targeting of which would provide an inhibition nor any examples of methods of preventing diseases or conditions as claimed.

The unpredictability of inhibiting expression of a target gene by RNA interference (RNAi), particularly in regards to the delivery of specific nucleic acids that mediate RNAi, is evident from literature that reflects the state of the art at the time of filing. While it is recognized that introduction of dsRNA that is targeted to a specific gene may result in inhibition of expression of the targeted gene, nucleic acid based therapies at the time of filing were highly unpredictable. Even to date, RNA interference is still recognized in the art as not enabled for therapeutic purposes. (See for example, Caplen (RNAi as a gene therapy approach. Expert Opin. Biol. Ther. 2003, Vol. 3, pgs. 575-586) for a review on the progression of RNA interference in mammalian cells and the state of the art of RNA interference for therapeutic purposes).

In regards to delivery of siRNA as a therapeutic, the post-filing art of Zhang et al. (Current Pharmaceutical Biotechnology 2004, vol. 5, p.1-7), who reviews the state of the art with regard to RNAi, has this to say about use in mammalian cells. "Use of siRNA in mammalian cells could be just as far-reaching, with the applications extending to functional genomics and therapeutics. But various technical issues must be addressed, especially for large-scale applications. For instance, dsRNA can be delivered to *C. elegans* by feeding or soaking, but effective delivery of siRNAs to mammalian cells will not be so simple."

The post-filing art of Caplen (2003) points out that, "Many of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system...". (see page 581) Coburn et al. also points out that the major impediment to using RNA interference as a therapeutic is that gene expression is transient and the delivery methods used for RNAi are not effective for therapeutic purposes (see for example p 754, first column, last paragraph). Those of skill in the art of RNA interference are optimistic about the potential of RNA interference as a therapeutic tool, but even with the advances made subsequent to the filing of the instant application, the field recognizes that therapeutic methods are not yet effective.

Post-filing art also describes the ongoing difficulties in using RNAi to treat disease. Check (Nature, 2003, vol. 425, p. 10-12) reports "...[S]cientists must figure out how to make RNAi therapies work. They are facing some formidable technical barriers, chief among which is the problem of getting siRNAs into the right cells. This is not a trivial issue, because RNA is rapidly broken down in the bloodstream and our cells don't readily absorb it through their membranes. And even when RNA gets into its target cell, scavenger proteins quickly chew it up." (see page 11, middle column, second full paragraph). Check describes that delivery methods are of concern to many researchers. In column 2 of page 11: " ...'The major hurdle right now is delivery, delivery, delivery' says Sharp" and in column 3 of the same page, "Khvorova believes

that the medical benefits of RNAi will be huge if the delivery issues can be resolved. 'But we've looked at a lot of the delivery methods that have been used for antisense, and so far I haven't been impressed,' she says."

Furthermore, Opalinska et al. (Nature Review, 2002, Vol. 1, p. 503-514) state, "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" and in column 2 of the same page, "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

Given this unpredictability, one of skill in the art would require specific guidance to practice the claimed methods *in vivo* in any organism (in particular in mammals and humans), with a resultant inhibitive, therapeutic or preventative outcome, as claimed. Applicant has not provided this guidance in regards to methods of delivery that can be used to target any particular cells of interest, organs or tissues such that the desired inhibitive, therapeutic or preventative effect, of inhibiting the function of any target

transcript, in any organism, is enabled. However, the claims as presently presented, read broadly on such a method.

Based on the state of the art, particularly in terms of the unpredictability of *in vivo* therapeutics set forth above, one of skill in the art would not know *a priori* whether introduction of a composition comprising an RNAi inducing entity and a cationic or modified cationic polymer delivery agent, into any organism, *in vivo*, would result in the successful targeting of any given target transcript. One of skill in the art would not know how to practice the instantly claimed methods of the invention, that require the administration of the above composition, to any cell of interest, tissue or organ of any organism in such a way that would ensure an amount sufficient to inhibit the target transcript (which could be any target transcript) was delivered to the proper cell for the appropriate amount of time to provide the claimed biological effect or to prevent a disease or condition as claimed. Methods of inhibiting gene expression using nucleic acids *in vivo* are unpredictable with respect to delivery of nucleic acid molecules such that said molecule is targeted to the appropriate cell/organ, at a bio-effective concentration and for a period of time such that said molecule is effective in attenuating or inhibiting expression of a target gene such that a therapy (or specified biological effect) is provided. The state of the art indicates that successful delivery of siRNAs to a target cell *in vivo*, such that the requisite biological effect is provided to the target cells/tissues/organs, must be determined empirically.

The specification does not provide the guidance required to overcome the art-recognized unpredictability in the delivery of nucleic acid therapeutics in general or for

the specific delivery of the claimed composition comprising an RNA-inducing entity and a delivery agent, into any organism, *in vivo*, that would result in the successful targeting of the target transcript. The field of RNA interference does not provide that guidance, such that any person skilled in the art would be able to practice the claimed methods without performing undue, *de novo*, trial and error experimentation to characterize and optimize a large number of variable parameters involved in the *in vivo* practice of nucleic acid therapeutics including, at least, a) the determination of what sequences would constitute RNAi inducing entities *in vivo*, that would include empirical determination of what RNAi inducing entities or siRNAs that are targeted to a target transcript would actually be effective at inhibiting expression of any target transcript, b) the mode of delivery of the composition comprising the RNAi inducing entity or siRNA and a delivery agent (including a delivery enhancing moiety that enhanced delivery to a cell of interest) to an organism that would allow it to reach any given target cell such that the desired inhibition, therapy or prevention was specifically provided, c) the amount of the claimed composition that is required by the method that would need to be delivered in order to allow targeting of the target transcript once it reached the proper cell, *in vivo* and d) ensuring the claimed the RNAi inducing entity or siRNA (that are required by the instant methods) remains viable in a cell for a period of time that allows targeting of the target transcript to an extent that there is a measurable and significant inhibitive, therapeutic or preventative effect. Each one of these variables would have to be empirically determined for each RNAi inducing entity or siRNA that is required by the composition that is required by the instantly claimed methods.

Thus, while the specification is enabling for methods of inhibiting, *in vivo*, in a mammal, the influenza virus NP or PA target transcript comprising administering, by intravenous injection to a mouse retro orbital vein, compositions comprising the cationic polymer, PEI, complexed siRNAs of the invention that are NP-1496 and PA2087 siRNAs, does not reasonably provide enablement for the full scope of what is claimed. One of skill in the art could not practice the invention commensurate in scope with what is now claimed, without undue, *de novo* trial and error experimentation. Additionally, the type of experimentation required to practice the invention more broadly that is exemplified is a factor in the enablement analysis, but is not dispositive. In this case, even if the nature of each experiment required to expand the scope of the enabled invention was considered standard (which it is not), it would be out weighted by the sheer quantity of experimentation required to practice the full scope of the claimed invention.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a)

11. Claims 49, 81, 83-84, 87-90 and 97-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCaffery et al. 2002 (Nature, Vol., 418: pp. 38-39 which is cited on the PTO Form 1449 filed 12/28/05 in the instant application), Aigner et al. (US 2004/0167087) and Ahn et al. (J. Cont. Release. Vol., 80: pp 273-282 which is cited on the PTO Form 1449 filed 12/28/05 in the instant application)

Claims 49, 81, 83-84, 87-90 and 97-98 are drawn to a method of treating or preventing a disease or clinical condition associated with overexpression or inappropriate expression of a transcript or excessive functional activity of a polypeptide encoded by the transcript comprising delivering a composition comprising an RNAi inducing entity and a cationic or modified cationic polymer delivery agent to a solid organ or tissue of a subject at risk of or suffering from a disease or clinical condition as above into the vascular system of the subject (claim 49); to a method of inhibiting the expression of a target transcript in a mammalian subject comprising administering to the

subject a composition comprising an RNAi inducing entity and a cationic or modified cationic polymer (claim 81) to at least one tissue or organ (claim 83) and to a method of treating or preventing a disease or condition associated with overexpression or inappropriate expression of a transcript or excessive functional activity of a polypeptide encoded by the transcript comprising providing a subject at risk or suffering from a disease or condition as above and administering a composition comprising administering an RNAi inducing entity targeted to the target transcript and a cationic or modified cationic polymer delivery agent (claim 84) intravenously using conventional fluid delivery (claims 87-88) wherein the delivery agent comprises a delivery enhancing moiety that is an antibody, antibody fragment or ligand (claims 89-90) wherein the RNAi inducing entity required by the methods of claim 81 and 84 respectively comprise a modified nucleotide (claims 98-99).

McCaffery et al. teach an *in vivo* method of inhibiting a human pathogenic RNA expressed from a Hepatitis C virus in mouse liver by administering an siRNA to the vascular system (pg. 38, col. 3 bridge to pg. 39, col. 2). McCaffrey et al. teach that siRNAs mimic intermediates in the RNA interference pathway and can silence genes in somatic cells without activating non specific suppression by dsRNA dependent protein kinase (pg. 38, col. 2). McCaffrey et al. teach that their method of RNAi delivery could be tailored to take advantage of developing viral and non viral gene transfer vectors in a clinical context (pg. 39, col. 2). The hydrodynamic injection protocol of McCaffery et al. is considered, in the absence of a limiting definition of "conventional fluid delivery" in the

instant specification, to reasonably read, as a method known in the prior art, on "conventional fluid delivery."

Aigner et al. teach an *in vivo* method of inhibiting the expression of PTN in human tumor xenotransplants that have been xenografted to mice by injection of an inhibitory nucleic acid composition comprising ribozymes complexed with a cationic polymer in athymic nude mice ribozyme and a cationic polymer (example 4). Aigner et al. teach that "Going beyond ribozymes, the complexing of RNA finally permits much more extensive, varied use for the stabilization of the most widely varying RNA molecules (pg. 2, [0018]) and that their invention describes that RNA molecules can be protected both extra and intracellularly from enzymatic and non enzymatic degradation by complexing with macromolecules based on PEI. Aigner et al. teach that the cationic polymer can be PEI and that PEI can be modified by cellular ligands for specific interaction and reception of the RNA-PEI-ligand complex (designated RNA-PEI-Q) in target cells, tissues or organs and that the ligand Q can be an antibody or antibody fragment (pg. 2, [0027], pg. 4, [0058-0059]). Aigner et al. teach that the RNA of their invention, that is complexed with the PEI, can be any RNA including a chemically synthesized RNA and that these RNAs can be chemically modified (pg. 2, [0028]).

Ahn et al. teach that non viral gene delivery systems such as cationic polymers of synthetic gene carriers are being investigated intensively to circumvent some of the problems encountered with the use of viral vectors (pg. 274, col. 1).

It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the instant invention was made, to practice a method of inhibiting the expression of

an HSV target transcript in the livers of mice using an siRNA injected into the vascular system (as taught by McCaffery et al.) wherein the method of delivery was tailored to take advantage of non-viral gene transfer vectors in a clinical context (as taught by McCaffery and Ahn et al.) that was complexed with PEI (as taught by Aigner et al.) because Aigner et al. teach that their invention describes that RNA molecules can be protected both extra and intracellularly from enzymatic and non enzymatic degradation by complexing with macromolecules based on PEI and provide a demonstration of the *in vivo* efficacy of inhibitory RNA molecules complexed with PEI. It is noted here that the non viral gene transfer vectors taught by McCaffery are considered to be a teaching of a non viral gene delivery system as that terminology is known and used in the prior art. This is evidenced by the teachings of Ahn et al. Additionally, it would have been *prima facie* obvious to one of ordinary skill in the art, at the time the instant invention was made, to practice this method wherein the delivery agent comprised a delivery enhancing moiety that was an antibody, antibody fragment or ligand (as taught by Aigner et al.) wherein the RNAi inducing entity comprised a modified nucleotide (as taught by Aigner et al.).

One of ordinary skill in the art would have been motivated to practice a method of inhibiting the expression of an HSV target transcript in the livers of mice using an RNA, that was an siRNA that was complexed with PEI (as taught by McCaffrey et al. and Aigner et al.) and injected into the vascular system (as taught by McCaffery) because the method of delivery taught by McCaffery could be tailored to take advantage of non-viral gene transfer vectors in a clinical context, because siRNA is an effective way to

silence genes without inducing a PKR response (as taught by McCaffrey) and because RNA molecules can be protected both extra and intracellularly from enzymatic and non enzymatic degradation by complexing with macromolecules based on PEI (as taught by Aigner et al.). One of ordinary skill in the art would have been motivated to practice this method wherein the delivery agent comprised a delivery enhancing moiety that was an antibody, antibody fragment or ligand (as taught by Aigner et al.) in order to increase specific interaction and reception of the RNA-PEI-ligand complexes in target cells, tissues or organs wherein the RNAi inducing entity comprised a modified nucleotide in order to further stabilize the RNAi entity from degradation (as taught by Aigner et al.).

One of ordinary skill in the art would have expected success in practicing a method of inhibiting the expression of HSV in the livers of mice using an siRNA that was complexed with PEI and injected into the vascular system because a successful method of inhibiting the expression of a HSV target transcript in livers of mice using siRNA was already known, because siRNA is an effective way to silence genes without inducing a PKR response (as taught by McCaffrey), because this method could be tailored to take advantage of non viral gene delivery systems *in vivo* in a clinical setting (as taught by McCaffrey et al.) and because non viral delivery systems for RNA molecules are provided by Aigner et al. to afford protection of administered RNA, *in vivo*, to both extra and intracellularly from enzymatic and non enzymatic degradation by complexing with macromolecules based on PEI. One of ordinary skill in the art would have expected success in practicing this method wherein the delivery agent comprised a delivery enhancing moiety that was an antibody, antibody fragment or ligand (as

taught by Aigner et al.) in order to increase specific interaction and reception of the RNA-PEI-ligand complexes in target cells, tissues or organs because successful embodiments are taught by Aigner et al. and would have expected success in practicing the above methods wherein the RNAi inducing entity comprised a modified nucleotide in order to further stabilize the RNAi entity from degradation (as taught by Aigner et al.)

Conclusion

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon B. Ashen whose telephone number is 571-272-2913. The examiner can normally be reached on 7:30 am - 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jba

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